Remarks

This AMENDMENT AFTER FINAL REJECTION is in response to the Official Action dated 10/23/06. A Petition for a ONE-MONTH Extension of Time is submitted to extend the time for response to 02/23/07.

Claims 25, 26, 28, 29, 31, 38, 40, 44, 47, 49, 50, 52, and 53 are currently in this case.

Claims 1-24, 27, 30, 32-37, 39, 41-43, 45, 46, 48, and 51 are cancelled.

Claims 25, 49, 50, 52, and 53 are currently amended herein.

Claims 26 remains in the case as originally filed.

The claims in the case which are independent claims are claims 25, 52, and 53.

Original claims and previously amended claims are ultimately dependent upon currently amended independent Claim 25.

Here are remarks relating to the Amendments to the Specification.

With respect to the amendment to the specification relating to Fig. 2, Fig. 2 clearly illustrates that the electrode is non-hollow and that the static layer of macromolecules is coated on the outside of the electrode.

Moreover, in a number of places in the specification, in the discussion of the prior art, there are clear teachings of a

desire to avoid problems associated with hollow hypodermic needles, and that the present invention is designed to avoid those problems associated with hollow hypodermic needles.

For example, in the specification, in a discussion of prior art, on page 3, lines 8-16 there is the following, to quote:

"Whenever a hollow hypodermic is employed in a tissue, the tissue is cut with a circular cut by the hollow hypodermic needle. As a result, when a patient receives hypodermic injection, the patient has considerable pain. To avoid such a circular cut, and to avoid the considerable pain involved, it would be desirable if a method for delivering molecules to biological cells were provided which does not employ a hypodermic needle."

Also, in the specification, in a discussion of prior art, on page 4, lines 20-22, there is the following, to quote:

"As mentioned above, avoiding the use hollow cylindrical needles would be desirable to avoid the pain involved therewith."

Moreover, in the specification, an object of the present invention is recited, on page 18, lines 3-6, in the following quote:

"Still a further object of the present invention is to provide a new and improved method and apparatus for delivery of macromolecules into cells which does not employ a hypodermic needle."

Also, in the specification, a provision of the present invention is recited, on page 44, lines 9-11, in the following quote:

"With the invention, a method and an apparatus for delivery of macromolecules into cells are provided which do not employ a hypodermic needle."

With respect to the amendment to the specification relating to Fig. 4, Fig. 4 clearly illustrates that the electrode is non-hollow and that the static layer of macromolecules is coated on the outside of the electrode. More specifically, Fig. 4 clearly shows a non-hollow long needle electrode 34 which is coated on the outside with static layer of electrode releasable molecules 44, e. g. macromolecules 18.

Now, here are remarks relating to the Amendments to the Claims.

Briefly, in the last Official Action dated 10/23/06, Examiner Fernandez rejected the remaining of the Applicant's claims under 35 USC § 103, as being unpatentable over Weidlich et al (5,103,837) in view of Hofmann (6,009,347), either as a pair of references together, or in combination with other references including Zewert et al (5,749,847), Widera et al (Journal of Immunology, 2000, 164:4635-4640), or Lerner (WO 97/18855).

Also, Examiner Fernandez rejected claims 49 and 50 relating to "product-by-process".

The current amendment of claims 25, 52, and 53 are submitted in response to the Official Action dated 10/23/06. These claims currently include the language:

"static layer of releasable **macromolecules** to be delivered **into biological cells**, in the tissues

penetrated by the electrode, by an **applied electric field applied to the biological cells** in the tissues penetrated by the electrode" [emphasis added].

In the Official Action dated 10/23/06, on page 2, in the second paragraph under "Claim Rejections", Examiner Fernandez states that the steroid, which is not a polymer, is delivered into biological cells penetrated by the electrodes. The Applicants do not dispute this. However, **and this is critical**, the polymers used to carry the steroid are not delivered into the biological cells. More specifically, the polymers remain in the interstitial portions of the tissues, outside the biological cells.

More specifically, the present AMENDMENT AFTER FINAL REJECTION is accompanied by the following Declaration: DECLARATION OF ALAN KING UNDER RULE 132. The Declaration addresses the rejections of the Applicant's claimed invention.

Attached to the Declaration are Alan King's Curriculum Vitae (Appendix A) and References Cited by Alan King in his Declaration (Appendix B).

Briefly, as understood by the Applicant's representative, in rejecting the Applicant's claimed invention, Examiner Fernandez reasons as follows. Weidlich et al (5,103,837) disclose electrodes coated with a steroid. Hofmann (6,009,347) discloses electroporation used to deliver biological materials (such as

macromolecules) into biological cells. Then, the Examiner concludes that it would be obvious to coat electrodes with biological materials (as taught by Weidlich et al (5,103,837) for delivery into biological cells using electroporation (as taught by Hofmann (6,009,347).

Briefly, as argued hereinbelow by the Applicant's representative, and as further explained in the DECLARATION OF ALAN KING UNDER RULE 132, the combination of Weidlich et al (5,103,837) and Hofmann (6,009,347) is not proper and nonobvious and should not prevent the patenting of the Applicant's claimed invention.

More specifically, it is pointed out that Weidlich et al (5,103,837) discloses a polymer (which is a macromolecule) which serves as a carrier for a steroid, which is a molecule, but not a macromolecule. Only the steroid (which is not a macromolecule) is delivered into the cells by diffusion. There is no teaching, and there is no reason why the hydrophilic polymer, which is a macromolecule, would itself be delivered into the cells. This is in sharp contrast with the Applicant's currently claimed invention wherein the macromolecules themselves are delivered into the biological cells.

Moreover, with Weidlich et al (5,103,837), the non-macromolecular steroid is not delivered into the cells by the applied electric field. Instead, the steroid is delivered into

the cells by diffusion. See claim 1 of Weidlich et al (5,103,837) which sets forth the essence of said patent.

Moreover, there is no reason to deliver any of the disclosed polymers into the cells because the disclosed polymers have no therapeutic function, for example the polymer polytetrafluoroethylene has no disclosed therapeutic function.

Generally, the Weidlich et al (5,103,837) polymers are used to provide a smooth surface to prevent cellular damage to heart tissue. The purpose of the Weidlich et al (5,103,837) polymers is diametrically opposed to delivering the polymers into heart cells. On the contrary, the Weidlich et al (5,103,837) polymers are used to minimize interaction with heart cells.

In review, clearly Weidlich et al (5,103,837) do not disclose delivering "**macromolecules**" into biological cells as provided by the Applicant's currently claimed invention.

Moreover Weidlich et al (5,103,837) do not disclose delivering any materials into biological cells "**in the tissues penetrated by the electrode, by an applied electric field applied to the biological cells in the tissues penetrated by the electrode**" as provided by the Applicant's currently claimed invention.

With respect to the "product-by-process" rejections of dependent claims 49 and 50, it is respectfully submitted that upon allowance of independent claim 25, such grounds for rejection will be made moot. Also, claims 49 and 50 are

currently amended herein to clarify the relationship between a "coating" and the steps carried out to apply the coating to the outside of the electrode.

In the Official Action dated 10/23/06, Examiner Fernandez cited Hofmann (6,009,347) which, as admitted by Examiner Fernandez, includes hollow needle electrodes. Now claim 25 includes the language:

> "A **non-hollow** needle electrode for penetration into tissues which includes an **outside coating**...".
>
> [emphasis added]

Briefly, Hofmann (6,009,347) discloses hollow needle electrodes that, when wetted, are wetted both inside and out. The "non-hollow" needle electrode of the currently claimed invention has only an "outside coating". Clearly, an inside coating is impossible with the "non-hollow" electrode.

More specifically, Hofmann (6,009,347) is directed to the arrangement and spacing of needle electrodes and the voltages applied to those needle electrodes. The needle electrodes are placed in a grid, and the voltages can be applied in a rotating pattern. There are two types of needle electrodes, both of which are used to penetrate tissues. One type of needle electrode is hollow, like a hypodermic needle; and the other type of needle electrode is solid throughout. Only the hollow needles are used to inject a treatment agent into the tissue to be treated. The

solid needle electrodes are simply counter electrodes, not used for applying a treating agent.

By having hollow needles used for injection of drugs into tissues, there is clearly no need for any Hofmann electrode to be pre-coated with a "coating having at least one static layer of releasable molecules to be delivered into biological cells" such as provided by the Applicant's claimed invention. With the Hofmann (6,009,347) electrodes, having a pre-coated electrode would be unnecessary and superfluous. Moreover, with the injection of treating material through the inside of a hollow needle, there is no reason to have the outside of a solid electrode to be pre-coated with a treating agent.

In addition, there is no disclosure in Hofmann (6,009,347) of eliminating the hollow needles used for drug injection. Also, there is no disclosure in Hofmann (6,009,347) of using any kind of substitute for the hollow needles used for drug injection. With the use of hollow needles for drug injection, there is simply no motivation to have pre-coated electrodes.

As stated in Hofmann (6,009,347), referring specifically to FIG. 2, the illustrated connector template is shown in use in treatment of a prostate cancer or the like. In this instance, the connector 22 is shown mounted on an elongated support rod 54 of an ultra-sound probe 56 which is shown inserted into the rectum of a patient. The sound probe is used to visualize the prostate and the location of the electrodes in the prostate. The template

is then in a position such that a plurality of needle electrodes 58, 60 and 62 in a first row are inserted through three of the horizontal through bores, as illustrated, and into the prostate of the patient. In this instance, two of the needle electrodes, 58 and 62, are illustrated as being solid needle electrodes and a center electrode 60 is shown to be hollow to enable the injection of molecules, such as a drug or therapeutic agent or other material [emphasis added].

A second, or lower row of needle electrodes 64, 66 and 68 is directly below the aforementioned electrodes and extend through the through bores of the connector template and into the prostate of the patient. In this instance, two outer needles, 64 and 68, are hollow to enable the injection of a therapeutic or other agent into the prostate of the patient. [emphasis added]. These may be left in place following the injection of the therapeutic agent and serve as the electrodes for the application of the electrical pulses to the tissue of the prostate or cancer cells within the prostate.

The hollow needles 60, 64 and 68 have outlet ports at the tip, as illustrated. For example, needle 64 is shown to have outlet ports 70 and 72. Similarly, outlet ports in needles 60 and 68 are shown but not given reference numerals. [emphasis added]

Clearly, Hofmann (6,009,347) does not contemplate any type of a pre-coated electrode for administration of any drug for electroporation thereof.

As a matter of fact, Hofmann (6,009,347) discusses the prior art of electroporation with electrodes, and nowhere in the discussion of the prior art is there a disclosure of the Applicant's claimed invention of electrodes being coated with a any coating, let alone an outside coating, having at least one static layer of releasable molecules to be delivered into biological cells.

More specifically, in the part of the specification of Hofmann (6,009,347) which discusses the prior art, Hofmann (6,009,347) states that with in vivo applications of electroporation, electrodes are provided in various configurations such as, for example, a caliper that grips the epidermis overlying a region of cells to be treated. Alternatively, needle-shaped electrodes may be inserted into the patient, to access more deeply located cells. In either case, after the implant agent is injected into the treatment region, the electrodes apply an electrical field to the region. [emphasis added].

Hofmann (6,009,347) also states that a number of experiments have been conducted to test therapeutic applications of electroporation for cancer treatment in a process now termed electrochemotherapy. This treatment is carried out by infusing an anticancer drug directly into the tumor and applying an electric field to the tumor between a pair of electrodes. [emphasis added].

In review, Hofmann (6,009,347) does not teach the use of a needle electrode, that is penetrated into tissue, that is pre-coated with any tissue treating agent, let alone a macromolecular treating agent. Moreover, in the four corners of Hofmann (6,009,347), there is no teaching of any way to administer a drug to be electroporated into biological cells in vivo other than the use of a hollow hypodermic needle, or the like, to inject or infuse a treating material into a tissue to be treated. Such limited treatment means disclosed in Hofmann (6,009,347), to a person with ordinary skill in the art, clearly teach away from employing a pre-coated non-hollow needle electrode to penetrate tissues for administering a macromolecule thereto.

In view of the above, the combination of Weidlich et al (5,103,837) and Hofmann (6,009,347) should not prevent the allowance of the Applicant's currently claimed invention.

Turning to Zewert et al (5,749,847), Widera et al (Journal of Immunology, 2000, 164:4635-4640), and Lerner (WO 97/18855), the following remarks are presented.

Zewert et al (5,749,847) disclose non-penetrating electrodes and a process of electroporation that is used to move a nucleotide component on the non-penetrating electrodes past the dead cells of the stratum corneum into an organism. Moreover, with Zewert et al (5,749,847), once the nucleotide component is in the organism below the stratum corneum, the nucleotide

component resides in the interstitial spaces between the cells of the organism and does not penetrate into the cells. Therefore, the non-penetrating electrodes of Zewert et al (5,749,847) do not cause the nucleotide component to be delivered into the cells of the organism.

As stated above, with Zewert et al (5,749,847), the electrodes that are employed for the electroporation do not penetrate into tissues. Instead, the Zewert et al (5,749,847) electrodes simply sit on the surface of the stratum corneum. The Zewert et al (5,749,847) electrodes are not present in the tissues that underlie the stratum corneum. This is in sharp contrast with the Applicant's currently claimed invention wherein the electrode is for penetration into tissues, and releasable macromolecules from a static layer coating on the electrode are delivered into biological cells in the penetrated tissues.

Clearly, Weidlich et al (5,103,837), Hofmann (6,009,347), or Zewert et al (5,749,847), either alone or in combination, should not be used to reject the Applicant's currently claimed invention. In this respect, it is respectfully submitted that the grounds for rejection of the Applicant's currently claimed invention based on Weidlich et al (5,103,837), Hofmann (6,009,347), or Zewert et al (5,749,847) be reconsidered and removed.

Turning to Widera et al (Journal of Immunology, 2000, 164:4635-4640), Widera et al use a three-step process for delivering a DNA vaccine into biological cells using three types of apparatuses. The first step is the use of a hypodermic needle (the first apparatus) to inject the DNA vaccine into tissues. The second step is to penetrate an electrode array (the second apparatus) into the tissues. The third step is to use an electric field generating apparatus (the third apparatus) to apply electric fields to the electrode array. The three-step process using the three types of apparatuses is substantially the same as the three-step process using three types of apparatuses that is set forth U. S. Patent No. 5,273,525 of Hofmann which is disclosed on page 3 of the Applicant's specification.

However, these teachings of Widera et al (Journal of Immunology) and U. S. Patent No. 5,273,525 of Hofmann are in sharp contrast with the Applicant's currently claimed invention wherein only two steps are used with only two apparatuses. More specifically, the first apparatus is the Applicant's electrode that is pre-coated with macromolecules on its outside surface; and the second apparatus is an apparatus for generating electric fields that are applied to the pre-coated electrode having an **"outside coating having at least one static layer of releasable macromolecules to be delivered into biological cells"**.

With the Applicant's currently claimed invention, the first step is to penetrate tissues with the coated electrode; and the

second step is to apply electric field onto the coated electrode in the penetrated tissues.

Clearly, Weidlich et al (5,103,837), Hofmann (6,009,347), or Widera et al (Journal of Immunology, 2000, 164:4635-4640), either alone or in combination, should not be used to reject the Applicant's currently claimed invention. In this respect, it is respectfully submitted that the grounds for rejection of the Applicant's currently claimed invention based on Weidlich et al (5,103,837), Hofmann (6,009,347), or Widera et al (Journal of Immunology, 2000, 164:4635-4640) be reconsidered and removed.

Turning to Lerner (WO 97/18855), Lerner (WO 97/18855) discloses electrodes (see page 26, lines 22-38) that are designed to have smooth, non-penetrating surfaces to deliver material into tissues or organs by iontophoresis. Iontophoresis does not accomplish the critical next step of getting material into cells using electroporation. There are many examples of iontophoresis being used for delivery of drugs into tissue. However, iontophoresis is not electroporation.

The tissues treated by Lerner (WO 97/18855) are not penetrated by the Lerner electrodes. Instead, the Lerner electrodes are placed on surfaces (such as skin) or are inserted (not penetrated) into blood vessels and body cavities where tissue treatment takes place. In addition, Lerner teaches that normal organ activity takes place while the Lerner electrode is

inserted. For example, on page 29, lines 25-32, there is a teaching that a nostril-inserted electrode has a hole in it so that normal breathing can be conducted.

Clearly, Lerner does not teach the Applicant's currently claimed invention which provides "A non-hollow needle electrode for penetration into tissues which includes an outside coating having at least one static layer of releasable macromolecules to be delivered into biological cells, in the tissues penetrated by the electrode, by an applied electric field applied to the biological cells in the tissues penetrated by the electrode".

Clearly, Weidlich et al (5,103,837), Hofmann (6,009,347), or Lerner (WO 97/18855), either alone or in combination, should not be used to reject the Applicant's currently claimed invention. In this respect, it is respectfully submitted that the grounds for rejection of the Applicant's currently claimed invention based on Weidlich et al (5,103,837), Hofmann (6,009,347), or Lerner (WO 97/18855) be reconsidered and removed.

No additional fees are required with respect to the type or number of claims.

A PETITION FOR REQUEST FOR EXTENSION OF TIME is filed concurrently herewith, along with a payment in the amount of $60.00.

In view of the foregoing, it is respectfully requested that claims 25, 26, 28, 29, 31, 38, 40, 44, 47, 49, 50, 52, and 53 be deemed allowable. If the Examiner believes otherwise, or has any comments or questions, or has any suggestions for putting the case in condition for final allowance, the Examiner is respectfully urged to contact the undersigned attorney of record at the telephone number below, so that an expeditious resolution may be effected and the case passed to issue promptly.

Respectfully submitted,

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Date

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